Similarly, the *clinical* utility of further detailed risk stratification of AF patients with prior stroke with different weights and score points (as proposed by the ATRIA score) is questionable, given that prior stroke is the most powerful single risk factor for recurrent stroke, and such patients should be given OAC without further risk stratification.

To work in a busy clinical practice, a clinical risk score needs to be simple, user-friendly, and practical. Risk scores are also meant to be reductionist to help therapeutic decision-making (i.e., anticoagulate or not); the CHA_2DS_2-VASc score allows the initial identification of "low-risk" AF patients who do not need any antithrombotic therapy, following which OAC can be considered for those with ≥1 stroke risk factor.

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REFERENCES

1. van den Ham HA, Klungel OH, Singer DE, Leufkens HG, van Staa TP. Comparative performance of ATRIA, $CHADS_2$, and CHA_2DS_2-VASc risk scores predicting stroke in patients with atrial fibrillation: results from a national primary care database. J Am Coll Cardiol 2015;66:1851–9.

2. Eckman MH, Singer DE, Rosand J, Greenberg SM. Moving the tipping point: the decision to anticoagulate patients with atrial fibrillation. Circ Cardiovasc Qual Outcomes 2011;4:14–21.

3. Lip GY, Skjoth F, Nielsen PB, Larsen TB. Non-valvular atrial fibrillation patients with none or one additional risk factor of the CHA_2DS_2-VASc score. A comprehensive net clinical benefit analysis for warfarin, aspirin, or no therapy. Thromb Haemost 2015;114:826–34.

REPLY: Comparing the ATRIA, $CHADS_2$, and CHA_2DS_2-VASc Scores for Stroke Prediction in Atrial Fibrillation

We tested the ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation), $CHADS_2$ (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke), and CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 65 to 74 years, female) stroke risk scores in the CPRD (Clinical Practice Research Datalink) cohort of incident atrial fibrillation (AF) patients not using oral anticoagulants (OAC) because these are the patients for whom physicians must make the OAC treatment decision (1). The mean patient follow-up of 0.74 years over a study period of 15 years indicates that a large proportion eventually received OAC. In the first year, the rate of warfarin prescription was 38%. The on- and off-warfarin cohorts did not differ much in stroke risk at index date. This illustrates that, in clinical practice, risk score-based decisions are not fully implemented.

An important message from our study (1) is that reported stroke rates in different cohorts can differ substantially. This is illustrated by national AF cohorts in Sweden and in Denmark (2,3), where the Danish point score-specific stroke rates are multiple times the Swedish rates. Considering the similarities in burden of disease and healthcare setting in these 2 Nordic countries, these differences in rates are likely largely explained by methodological choices in the study, such as outcome definition (4). Our paper also illustrated that optimal risk score cut points will differ with different rates. It will be important to standardize analytic approaches to be sure differences in reported stroke rates reflect truly different stroke rates.

A major advantage of the ATRIA score over the CHA_2DS_2-VASc score is its use of additional age categories and formal statistical weighting of these risk factors. The CHA_2DS_2-VASc score was not founded on a formal statistical approach. As a result, AF patients can have a CHA_2DS_2-VASc score of 1 from hypertension or from being age 65 to 74 years; the former risk factor conveys little additional stroke risk, whereas the latter increases risk multifold. The better risk prediction of the ATRIA score is also clinically valuable at higher point scores in patients with contraindications to OAC, where accurate absolute stroke risk must be balanced against risk of toxicity.

The argument of the importance of simplicity of a risk score is in our opinion not valid in a world in which technology is completely integrated in our daily lives. A patient who will be put on a long-term treatment deserves the best informed decision that optimally integrates patient data. Undoubtedly, we will build on current risk scores (e.g., with biomarkers). It is important that we start with our most rigorously developed and accurate AF stroke risk score.

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REFERENCES

1. van den Ham HA, Klungel OH, Singer DE, Leufkens HG, van Staa TP. Comparative performance of ATRIA, $CHADS_2$, and CHA_2DS_2-VASc risk scores predicting stroke in patients with atrial fibrillation: results from a national primary care database. J Am Coll Cardiol 2015;66:1851–9.

2. Friberg L, Rosenqvist M, Lip GYH. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. Eur Heart J 2012;33:1500–10.

3. Olesen JB, Lip GYH, Lindhardsen J, et al. Risks of thromboembolism and bleeding with thromboprophylaxis in patients with atrial fibrillation: a net clinical benefit analysis using a 'real world' nationwide cohort study. Thromb Haemost 2011;106:739.

4. Friberg L, Skeppholm M, Terént A. Benefit of anticoagulation unlikely in patients with atrial fibrillation and a CHA_2DS_2-VASc score of 1. J Am Coll Cardiol 2015;65:225–32.

Recent Diabetes and Atrial Fibrillation Report Diverges From Pre-Existing Evidence

We read with interest the study by Ashburner et al. (1), investigating associations between duration of diabetes, glycemic control, and risk of ischemic stroke in patients with atrial fibrillation (AF) in the ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) cohort.

They found that duration of diabetes is an important predictor of ischemic stroke in patients with AF, suggesting that an arbitrary duration threshold of ≥3 years may be a useful cut-off. These findings serve partly as valuable confirmation of observations from another recent analysis including >17,000 patients with AF and concomitant diabetes that investigated a similar issue (2). Here, the risk of a composite outcome of ischemic stroke or systemic embolism according to diabetes duration exhibited a linear dose-response relationship, with the highest risk observed among patients with diabetes duration ≥15 years. These previous data do not support a risk threshold at 3 years of duration as observed in the ATRIA study.

The ATRIA study also used glycemic control as exposure. Perhaps surprisingly, no clear positive associations between hemoglobin A1c (HbA1c) levels and ischemic stroke were observed. Suggested explanations included the unique stroke etiology inflicted by AF that may be unaffected by HbA1c, and the short follow-up period of ≈2.5 years (1,3). However, another recent report including >11,000 patients opposes these explanations, in which a clear dose-response relationship between HbA1c and risk of incident stroke or transient ischemic attack was observed, despite a mean follow-up of <1 year (4). The relatively smaller ATRIA sample size and the exclusion of follow-up time without HbA1c information may have limited the possibility of detecting a similar signal.

In summary, the results from the ATRIA study should be interpreted with caution and in light of the pre-existing evidence investigating similar matters. Nonetheless, the results re-emphasize the important observation that the dichotomization of diabetes in many available AF risk scores is simplistic, and that subdividing existing score components would provide new avenues for more accurate and individualized risk calculations.

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REFERENCES

1. Ashburner JM, Go AS, Chang Y, et al. Effect of diabetes and glycemic control on ischemic stroke risk in AF patients: ATRIA study. J Am Coll Cardiol 2016;67:239–47.